

What is claimed is:

1. A pharmaceutical composition for inhibiting cellular apoptosis, the composition comprising at least one apoptosis inhibiting compound that can modulate caspase-independent apoptosis.

2. The pharmaceutical composition of claim 1 further comprising a pharmaceutical acceptable excipient.

3. The pharmaceutical composition of claim 1 further comprising a mixture of apoptosis inhibiting compounds, wherein the apoptosis inhibiting compounds in the mixture can modulate caspase-independent apoptosis.

4. The pharmaceutical composition of claim 1, wherein the apoptosis inhibiting compound comprises the general structure shown in Fig. 1a, where R_1 is selected from the group consisting of a nitro group, a carboxy group, a hydroxide, an aliphatic group, an aromatic group, an acyl group, an alkoxy group, an alkylene group, an alkenylene group, an alkynylene group, a hydroxycarbonylalkyl group, an anhydride, an amide, an amine, and a heterocyclic aromatic group.

5. The pharmaceutical composition of claim 4, wherein the apoptosis inhibiting compound is the structure shown in Fig. 1b.

6. The pharmaceutical composition of claim 1, wherein the apoptosis inhibiting compound comprises the general structure shown in Fig. 2a where R_1 is selected from the group consisting of a nitro group, a carboxy group, a hydroxide, an aliphatic group, an aromatic group, an acyl group, an alkoxy group, an alkylene group, an alkenylene group, an alkynylene group, a hydroxycarbonylalkyl group, an anhydride, an amide, an amine, and a heterocyclic aromatic group.

7. The pharmaceutical composition of claim 1, wherein the apoptosis inhibiting compound is the structure shown in Fig. 2b.

8. The pharmaceutical composition of claim 1, wherein the apoptosis inhibiting compound comprises the general structure shown in Fig. 3a, where R₁ is selected from the group consisting of a nitro group, a carboxy group, a hydroxide, an aliphatic group, an aromatic group, an acyl group, an alkoxy group, an alkylene group, an alkenylene group, an alkynylene group, a hydroxycarbonylalkyl group, an anhydride, an amide, an amine, and a heterocyclic aromatic group.

9. The pharmaceutical composition of claim 8, wherein the apoptosis inhibiting compound is the structure shown in Fig. 3b.

10. The pharmaceutical composition of claim 1, wherein the apoptosis inhibiting compound comprises the general structure shown in Fig. 4a, where R₁ is selected from the group consisting of a nitro group, a carboxy group, a hydroxide, an aliphatic group, an aromatic group, an acyl group, an alkoxy group, an alkylene group, an alkenylene group, an alkynylene group, a hydroxycarbonylalkyl group, an anhydride, an amide, an amine, and a heterocyclic aromatic group.

11. The pharmaceutical composition of claim 10, wherein the apoptosis inhibiting compound is the structure shown in Fig. 4b.

12. A method for inhibiting caspase-independent apoptosis in a cell comprising:
contacting a cell having Omi/HtrA2 activity with at least one apoptosis inhibiting compound, such that the apoptosis inhibiting compound interacts with Omi/HtrA2 to inhibit the activity of Omi/HtrA2, wherein the inhibition of Omi/HtrA2 activity reduces apoptosis in the cell; and
monitoring the inhibition of apoptosis.

13. The method of claim 12, wherein the step of contacting the cell comprises contracting the cell *in vivo*.

14. The method of claim 12, wherein the step of contacting the cell comprises contacting the cell *in vitro*.

15. The method of claim 12, wherein the apoptosis inhibiting compound is selected from the group consisting of the structure shown in Fig. 1a, Fig. 2a, Fig. 3a and Fig. 4a.

16. The method of claim 12, wherein the apoptosis inhibiting compound is the structure shown in Fig. 1b.

17. The method of claim 12, wherein the apoptosis inhibiting compound is the structure shown in Fig. 2b.

18. The method of claim 12, wherein the apoptosis inhibiting compound is the structure shown in Fig. 3b.

19. The method of claim 12, wherein the apoptosis inhibiting compound is the structure shown in 4b.

20. A method of inhibiting Omi/HtrA2 activity, comprising:
contacting a cell having Omi/HtrA2 activity with an apoptosis inhibiting compound;
and
monitoring the inhibition of Omi/HtrA2 activity.

21. The method of claim 20, wherein the step of contacting the cell comprises contacting the cell *in vivo*.

22. The method of claim 20, wherein the step of contacting the cell comprises contacting the cell *in vitro*.

23. The method of claim 20, wherein the apoptosis inhibiting compound is selected from the group consisting of the structure shown in Fig. 1a, Fig. 2a, Fig. 3a and Fig. 4a.

24. The method of claim 20, wherein the apoptosis inhibiting compound is the structure shown in Fig. 1b.

25. The method of claim 20, wherein the apoptosis inhibiting compound is the structure shown in Fig. 2b.

26. The method of claim 20, wherein the apoptosis inhibiting compound is the structure shown in Fig. 3b.

27. The method of claim 20, wherein the apoptosis inhibiting compound is the structure shown in Fig. 4b.

28. The method of claim 20, wherein the step of monitoring Omi/HtrA2 activity comprises monitoring a change in fluorescence of an Omi/HtrA2 substrate coupled to a fluorescent marker.

29. The method of claim 20, wherein the step of monitoring the inhibition of Omi/HtrA2 activity further comprises monitoring apoptosis of the cell.

30. A method for modifying a disorder associated with caspase-independent apoptosis comprising:

administering a therapeutically effective amount of a composition comprising at least one apoptosis inhibiting compound such that the apoptosis inhibiting compound interacts with Omi/HtrA2 to inhibit the activity of Omi/HtrA2, wherein the inhibition of Omi/HtrA2 activity reduces apoptosis in the cell; and

monitoring the amelioration of the disorder by measuring the change in caspase-independent apoptosis.

31. The method of claim 30, wherein the disorder is selected from the group consisting of kidney failure, heart failure, heart attack, stroke, neurodegenerative disease, cancers and tumors.
- 5 32. A method of preventing tubular cell death, comprising:
administering an apoptosis inhibiting compound, wherein the apoptosis
inhibiting compound interacts with Omi/HtrA2 such that the apoptosis inhibiting compound
interacts with Omi/HtrA2 to inhibit the activity of Omi/HtrA2, wherein the inhibition of
Omi/HtrA2 activity prevents tubular cell death; and
10 monitoring the prevention of tubular cell death.
33. The method of claim 32, wherein the apoptosis inhibiting compound is selected from
the group consisting of the structure shown in Fig. 1a, Fig. 2a, Fig. 3a and Fig. 4a.
- 15 34. The method of claim 32, wherein the apoptosis inhibiting compound is the structure
shown in Fig. 1b.
35. The method of claim 32, wherein the apoptosis inhibiting compound is the structure
shown in Fig. 2b.
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36. The method of claim 32, wherein the apoptosis inhibiting compound is the structure
shown in Fig. 3b.
37. The method of claim 32, wherein the apoptosis inhibiting compound is the structure
25 Fig. 4b.
38. The method of claim 32, wherein the tubular cell death is associated with the proximal
tubules of the kidney.
- 30 39. The method of claim 38, wherein the tubular cell death results in renal apoptosis.

40. The method of claim 32, wherein the tubular cell death results in renal ischaemia.

41. A method for identifying a substrate associated with caspase-independent apoptosis, comprising:

5 contacting a cell with recombinant Omi/HtrA2, wherein the recombinant Omi/HtrA2 has proteolytic activity;

 comparing the results of the incubated cell extract with a control sample that has not been incubated with recombinant Omi/HtrA2; and

 monitoring a change in the electrophoretic mobility of a protein in the cell extract
10 incubated with recombinant Omi/HtrA2, such that a change in electrophoretic mobility of the protein indicates that the protein is a substrate of Omi/HtrA2, thereby identifying a substrate associated with caspase-independent apoptosis.

42. The method of claim 41, wherein the step of contacting the cell comprises contacting
15 the cell *in vivo*.

43. The method of claim 41, wherein the step of contacting the cell comprises contacting the cell *in vitro*.

20 44. The method of claim 41, further comprising monitoring the disappearance of the protein in the cell extract incubated with recombinant Omi/HtrA2.

45. The method for claim 41, wherein the cell extract is obtained from a kidney.

25 46. The method for claim 41, wherein the substrate associated with caspase-independent apoptosis is 14-3-3

47. The method for claim 41, wherein the substrate associated with caspase-independent apoptosis is Annexin V.

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48. A method for identifying a compound that inhibits caspase-independent apoptosis, comprising:

contacting the candidate compound with a substrate coupled to a fluorescent marker in the presence of recombinant Omi/HtrA2, wherein the recombinant Omi/HtrA2 has proteolytic activity against the substrate; and

monitoring the change in fluorescence, whereby a candidate compound is identified as being an inhibitor of caspase-independent apoptosis if the candidate compound inhibits or blocks the proteolytic activity of recombinant Omi/HtrA2.

49. The method of claim 48, wherein substrate is an Omi/HtrA2 substrate selected from the group consisting of 14-3-3 and annexin V.

50. The method of claim 48, wherein substrate is casein.

51. The method of claim 48, wherein the fluorescent marker is selected from the group consisting of fluorescein isothiocyanate (FITC), cyanine dye-5 (CY5), cyanine dye-3 (Cy3), cyanine dye-7 (Cy7), allophycocyanin (APC), tetramethyl rhodamine isothiocyanate (TRITC), and phycoerythrin (PE).

52. The method of claim 48, wherein the fluorescent marker is FITC.

53. The method of claim 48, wherein the recombinant Omi/HtrA2 is MBP-Omi₁₃₄₋₄₅₈